REMARKS

The Office Action of February 27, 2001 presents the examination of claims 1-10, 14, and 15. Claims 1-5, 7, 10, 14, and 15 are amended. No new matter is inserted into the application.

Request for Interview

Upon receipt of this Reply, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the law offices of Birch, Stewart, Kolasch & Birch, LLP, (703) 205-8000, to arrange for a personal interview for purposes of expediting prosecution of the present application.

Claim Rejections Maintained

Claim 10

The Examiner maintains the rejection of claim 10 for allegedly not being disclosed in the specification, as well as maintains the denial of priority under 35 U.S.C. 119 (a-e). Applicants respectfully traverse. Reconsideration of the claim and withdrawal of the instant rejection and denial of priority are respectfully requested.

The Examiner remains convinced that "a method for prognostication of cancer comprising sequencing the entire coding region of a DNA encoding a p53 protein...was not contemplated by the inventors at the time the application was filed." Again, Applicants respectfully disagree.

As stated in the Reply filed on October 10, 2001, the specification on page 6 reads "...by sequencing at least throughout the part or parts of the p53 gene which encode biologically functional domains...." Applicants strongly submit that this sentence does indeed contemplate the entire open reading frame, and that the Examiner relies on pure semantics to improperly maintain the rejection. The biologically functional domains of a protein are encoded by exons. Thus, contrary to the Examiner's assertions, the cited sentence does support the scope of the claims.

For these reasons, Applicants respectfully submit that the claim 10 complies with 35 U.S.C. § 112, first paragraph, and respectfully request that the instant rejection be withdrawn. Further, Applicants respectfully traverse the denial of priority for reasons of record, and request withdrawal of the denial.

Claim 15

The Examiner maintains the rejection of claim 15 under 35 U.S.C. § 102(e) for allegedly being anticipated by Diamandis '283. Applicants respectfully traverse. Reconsideration of the claim and withdrawal of the instant rejection are respectfully requested.

In response to the Examiner's remarks, Applicants amend claim 15 from "the parts of a cancer-related p53 protein" to "all exons of a cancer-related p53 protein." This amendment clarifies that all of the biologically functional domains, which are exons, of p53 are sequenced in the inventive method, whereas Diamandis '283 only teaches sequencing of a few select exons.

For this reason, Diamandis '283 fails to anticipate the present invention. Withdrawal of the instant rejection is therefore respectfully requested.

Claims 1-10 and 14

The Examiner maintains the rejection of claims 1-10 and 14 for allegedly being obvious over Elledge et al. and Callahan in view of Diamandis et al. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that no arguments were presented in the Reply of October 10, 2001. Applicants respectfully disagree. Apparently, the Examiner failed to consider the arguments presented on page 8 of the Reply, stating that none of these references disclose sequencing the entire p53 gene. Applicants reiterate these remarks below.

The Examiner acknowledges, "Elledge et al. and Callahan et al. differ from the present invention in that they do not detect p53 mutations by sequencing the entire coding region of the gene." Thus, the Examiner relies on Diamandis '283 to make up for the deficiencies of Elledge et al. and Callahan et al. However, the Examiner has improperly made an obvious rejection based upon a combination of these three references.

Specifically, the Examiner must consider the prior art as a whole, including portions that lead away from the claimed invention (MPEP 2141.02). The disclosure of Diamandis '283, as a whole, teaches away from the present invention. In column 2, lines 23-26, Diamandis states, "These rapid DNA-based techniques have used to detect mutations, but because they are so labor intensive, that large scale screening tests are impractical." Continuing at column 2, line 28 onwards, "Thus, the existing methods of diagnosis have been frustratingly unsatisfactory.

Continuing at column 2, line 28 onwards, "Thus, the existing methods of diagnosis have been frustratingly unsatisfactory. Researchers have used either immunoassay or DNA analytical methods...". Line 31, "Sequencing is expensive and so it may be desirable to use a sub-hierarchy within this level to reduce the likelihood of having to sequence all the exons." These statements clearly teach away from the present invention. At line 61, Diamandis '283 discloses, "Alternatively, the user may choose to test all exons simultaneously at once." However, this statement refers to PCR rather than sequencing, and therefore this statement cannot be applied to the present invention. Thus, the teachings of Diamandis '283 cited by the Examiner in support of the obviousness rejection cannot be sustained when even Diamandis '283 clearly proclaims that they are not satisfactory.

For these reasons, Applicants submit that the combination of Elledge et al. and Callahan in view of Diamandis et al. fails to make the present invention obvious. Withdrawal of the instant rejection is therefore requested.

New Grounds of Rejection

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner issues a new rejection of claims 1-10, 14 and 15 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 1, 14 and 15 are rejected for reciting the phrase "biologically functional domains." The "biologically functional domains" are exons of the nucleotide sequence. Claims 1, 14, and 15 are amended to clarify this matter. Thus, the instant rejection is overcome.

Claims 1, 14, and 15 are rejected because the phrase "the parts of a cancer-related..." allegedly lacks antecedent basis. In response to the Examiner's remarks, "the parts" is deleted from said claims. Thus, the rejection is overcome.

Claims 1, 14, and 15 are rejected for reciting "the nucleotide sequence of a part of p53 protein." In response to the Examiner's remarks, Applicants amend the claims to "the nucleotide sequence of all exons of a cancer-related p53 nucleic acid." Thus, the instant rejection is overcome.

Claims 1, 14, and 15 are rejected because step "d" is an inactive step, and allegedly does not correlate with the preamble. In response to the Examiner's remarks, Applicants amend the claims to overcome these rejections.

Claims 1, 14, and 15 are rejected for reciting "prognostication of the development of neoplasia." The Examiner asserts that the specification only supports prognosis for a patient already diagnosed with cancer. Applicants advise the Examiner that claim 1 recites "in a human patient having a neoplasia," and thusly is accurate.

Claim 2 is rejected for reciting the typing of a p53 mutation. In response to the Examiner's remarks, Applicants amend the claim to clarify that the method of claim 1 further comprises a typing step. Thus, the instant rejection is overcome.

Claim 3 is rejected for lacking appropriate antecedent bases. In response to the Examiner's remarks, claim 3 is amended to conform to antecedent requirements. Thus, the instant rejection is overcome.

Claim 10 is rejected for allegedly being unclear as to which steps are included in the claim, lacking appropriate antecedent bases, and being drawn to an assay method, allegedly

without a correlation step. In response, claim 10 is amended to overcome these rejections based upon the Examiner's remarks.

Based upon the above, Applicants respectfully submit that the amended claims fully comply with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 2 and 3 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not described in the specification, as well as under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Written Description

Specifically, the Examiner asserts that the specification does not support an embodiment of the claimed invention wherein "a prognosis is made of the biological aggressiveness and/or metastatic potential of a neoplasia based on a determination of

whether a tumor has a p53 mutation and whether a patient is node positive or not."

In response to the Examiner's remarks, Applicants amend claims 2 and 3 to clarify their meanings. As these amendments address the issues of written description raised by the Examiner, Applicants respectfully request withdrawal of the instant rejection.

Enablement

The Examiner also asserts that claim 3 is not enabled for every type of cancer. Specifically, the specification only provides evidence for breast cancer. The Examiner points to two references, which suggest that different types of cancers have different correlations of p53 mutations, and therefore "a correlation between p53 mutation and biological aggressiveness and/or metastatic potential is not predictable for all cancers."

In response to the Examiner's remarks, Applicants amend claim 3 limiting the scope of claim 3 to breast cancer only. As such, the instant rejection is overcome.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejects claim 15 for allegedly being anticipated by Thorlacius et al. (*Cancer Res.*, 53:1637-1641 (1993)). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Thorlacius et al. discloses the DNA sequencing of exons 5, 7, and 8 to determine p53 mutations. However, Thorlacius et al. fails to disclose a method for prognostication of the development of neoplasia by sequencing all of the exons of p53. Claim 15 is amended to clarify that all of the p53 exons are sequenced, rather than just a select few, as taught of Thorlacius et al.

For these reasons, Thorlacius et al. fails to anticipate the present invention. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 2, 4-7 and 14 for allegedly being obvious over Hedrum et al. in view of Elledge et al. and Callahan. Applicants respectfully traverse. Reconsideration of

As stated above, Elledge et al. and Callahan et al. fail to detect p53 mutations by sequencing the entire coding region of the gene. Again, the Examiner attempts to make up for the deficiencies of Elledge et al. and Callahan et al. by adding Hedrum et al. However, Hedrum et al. merely teaches the sequencing of exons 4-9. Thus, absolutely no reference teaches a method for prognostication of the development of neoplasia by sequencing each and every exon of p53.

As such, the present invention is not unpatentable over the combination of references cited by the Examiner. Withdrawal of the instant rejection is therefore respectfully requested.

Overall, the present invention possesses significant patentable features that the cited prior art references do not possess. Furthermore, Applicants submit the instant claims are fully in compliance with 35 U.S.C. § 112, first and second paragraphs. All of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Favorable action on the merits of the present application is thereby requested.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for an extension of one (1) month to June 27, 2000 for the period in which to file a response to the outstanding Office Action. The required fee of $110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the following claims:

1. (Five Times Amended) A method for prognostication of the development of neoplasia and providing [obtaining] guidance for treatment in a human patient having a neoplasia comprising:

a) determining a nucleotide sequence of all exons [the parts] of a cancer-related p53 nucleic acid [protein] which encode biologically functional domains from genomic DNA or cDNA derived from a human neoplastic tissue or body fluid;

b) analyzing the nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on

(i) the presence or absence of a mutation, and

(ii) whether the patient is node positive or not; and

d) [using the results of steps c)(i) and c(ii) in combination for] prognosticating the development of the neoplasia by combining the results of steps c)(i) and c)(ii) and providing guidance for the treatment of the patient.

2. (Three Times Amended) The method of claim 1, [wherein a mutation is typed as a] further comprising the step of typing the

mutation of step c)(ii) into a group selected from the group consisting of a missense mutation, a nonsense mutation, a deletion, and an insertion.

3. (Twice Amended) The method of claim 2, further comprising determining [wherein] the presence[,] and position [and type] of the [a] mutation [found is used to categorize the] and categorizing biological aggressiveness and/or metastatic potential of the neoplasia based upon the presence, position, and type of mutation,

wherein said neoplasia is breast cancer.

4. (Three Times Amended) The method of claim 1 wherein a an exon or exons [part or parts] of the sequenced nucleic acid [gene] encode a DNA binding domain.

5. (Twice Amended) The method of claim 1 wherein evolutionary conserved regions of the nucleic acid [gene] are analyzed.

7. (Twice Amended) The method of claim 6, wherein said neoplasia [sample] originates from a breast neoplasia.

10. (Three Times Amended) The method of claim 1, [comprising the following steps:

a) obtaining a sample containing genomic DNA or cDNA encoding p53

b) amplifying the sequences corresponding to the complete coding region of the p53 gene;

c) sequencing the complete coding region sequence obtained in step b); and

d) detecting the products from the sequencing reactions in] wherein step a) is carried out using an automated nucleic acid sequencer, computer software optionally being used to (i) track samples and control process steps and/or (ii) to aid in and/or interpret sequence data obtained.

14. (Three Times Amended) A method for prognostication of the development of neoplasia in a human patient having a neoplasia comprising:

a) determining the nucleotide sequence of all exons [the parts] of a cancer-related p53 nucleic acid [protein] which encode biologically functional domains from genomic DNA or cDNA derived from a human neoplastic tissue or body fluid;

b) analyzing the nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on

(i) the presence or absence of a mutation, and

(ii) whether the patient is node positive or not; and

d) [using the results of steps c)(i) and c(ii) in combination for] prognosticating the development of the neoplasia by combining the results of steps c)(i) and c)(ii).

15. (Three Times Amended) A method for prognostication of the development of neoplasia in a human patient having a neoplasia comprising:

a) determining the nucleotide sequence of all exons [the parts] of a cancer-related p53 nucleic acid [protein] which encode biologically functional domains from genomic DNA or cDNA derived from a human neoplastic tissue or body fluid;

b) analyzing the entire nucleotide sequence determined in step a) for the presence of mutations; and

c) classifying the neoplasia into different subgroups depending on the presence or absence of a mutation; and

d) [using the results of steps c) alone for] prognosticating the development of the neoplasia by analyzing the results of step c) only.